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- (54) **Pharmaceutical compositions
containing allyl isothiocyanate**

(57) Topical pharmaceutical compos-
itions having rubefacient activity
comprise allyl isothiocyanate ("mus-
tard oil") and a vegetable oil.

ERRATUM

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Page 5, line 65, *after of* (first occurrence) *insert* oil of

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SPECIFICATION

Composition and process for the cure of internal wounds and inflammation

5 This invention relates to a new composition and a new technique for obtaining new curative effects from the composition.

10 Almost every internal disease of man and lower animals is due to internal inflammations or injuries. They result from physical, chemical or biological agents. The latter ones are by far the most important, such pathogenic biological agents including bacteria, protozoa, 15 fungi and viruses, which give rise to infections. An infectious disease is therefore a morbid condition caused by pathogenic agents. It may be localized in a single part of the body or the blood flow may spread it throughout the body.

20 Inflammation is a local reaction to the infection. It consists of a morphological alteration of inflamed tissues, so-called vessel congestion, which takes place in two stages, with 25 ischemia, i.e. a local anemia produced by local obstacles to the arterial flow, followed by dilation and resulting hyperemia. The affected organism mobilizes phagocytes; they are transmitted through the blood to the site of 30 inflammation and, together with local histiocytes (fixed macrophages), they struggle against pathogenic germs, trying to enclose, ingest and destroy them. Blood that is in such a phase has a throbbing character, gradually 35 releasing its tension, achieving a kind of stasis with resulting congestion. In this second phase its components (erythrocytes and leukocytes which are usually mixed together) form two separated groups; erythrocytes being in 40 the middle and leukocytes along the vessel walls.

From the dilated pores of the blood vessels the leukocytes and pathogenic germs seep into the tissues.

45 Vasodilatation, permeabilization and exudation follow an inflammation. The process of reparation and reconstruction, which takes place at the end of an inflammatory process, occurs according to a fixed pattern, i.e. the 50 formation of granulation tissue.

An internal injury is, on the other hand, an anatomical damage of any internal tissue or organ of the body resulting from physical agents (fractures), chemical agents or patho- 55 genic infection.

60 Diathesis is different from both inflammation and internal injury. It is a constitutional predisposition or tendency to a particular disease or affliction. Some patients, through congenital or hereditary causes, have some organs or tissues, which are like a ground where certain diseases take root with greater facility. Diathesis, therefore, is not an actual morbid condition in itself, but a bodily constitution 65 which is predisposed to a disease, or class of

diseases. Lithic diathesis, for instance, describes the condition of patients prone to the formation of calculi in the gall bladder, kidneys, vesica, prostate, and so on.

70 Since organic defenses are not always able to wipe out a morbid attack, medical science has conducted a vast amount of research to find means to aid the body's defenses.

The aim of chemotherapeutical research is 75 the discovery of molecules which are as dangerous as possible to infectious agents and as harmless as possible to humans.

After the introduction of sera and vaccines, an important chemotherapeutic discovery was 80 the preparation of sulfa drugs, whose effect is to reduce the activity of the metabolites of pathogenic germs, in order to weaken and make them easier prey of the natural defenses of the patient. The discovery of antibiotics 85 followed.

Antibiotic treatment takes advantage of antagonisms among different germs and different species, giving back the viable balance to the attacked organism. The action of antibiotics varies from antibiotic to antibiotic. Some 90 interfere with the growth of micro-organisms and with cell division, some with microbial respiration, some with the utilization of essential metabolites.

95 Another kind of organic defense against microbial infections or lesions is the use of drugs having therapeutic properties. These drugs are split up into two groups; elective and non-elective drugs, the former acting on 100 certain organs or tissues, the latter on every organ or tissue.

In spite of the remarkable progress achieved in the treatment of internal injuries and inflammations by the introduction of new remedies, we are far, however, from achieving the final goal. Particularly, sulfa drugs and antibiotics, which proved invaluable in the treatment of acute infectious diseases are not very effective in the struggle against chronic diseases, for humans tend to assuetude in cases of a long-term treatment. Moreover, a specific remedy is lacking in many cases, such as in lithiasis and several organic disorders. Finally, there are some cases, in which, even though 110 there are drugs for the treatment of certain diseases, their toxicity prevents their use at an adequate concentration. Consequently, many diseases are still incurable. Also diathesis, being ignored rather than treated, too often fatally develops from a predisposition stage to a specific disease. Chronic infirmity, as a permanent weakness, continues to threaten not only the health, but the life itself of its victims.

125 The only refuge in many cases is to resort to a surgical operation. But, apart from not always being possible, it must be pointed out that, even when the operation is practicable, surgery often becomes a demolishing process, 130 with a severe impairment of the functional

capabilities of the patient.

The gaps touched on above, although they cover nearly every therapeutical field, are particularly glaring for nervous and mental diseases. Here the treatment is highly ineffectual and often the only solution is a segregation of the patient from the human community.

To sum up, in spite of great progress, several deficiencies remain in the treatment of internal injuries and inflammations, of diathesis and of nervous and mental diseases.

The present invention compensates for some of the inadequacies of present-day therapy by the use of a chemical substance in conjunction with a special technique. The new discovery presupposes that in any microbic attack and in any dysfunction of the organs and tissues, the natural defenses constitute the base for defeating the illness and that medicines and remedies are merely subsidiary means of assisting such a defense. The corollary arrived at from this premise is that the principal task of therapy is not only to reinforce this reaction, but also to recreate it by artificial means, when the body is not able to do so independently.

On the basis of existing knowledge we can now provoke such a natural reaction in the superficial blood vessels. In fact it is known that heat administered by means of compresses, hydrotherapy, mud-baths, vapor or electricity on a part of the body produces a dilation of the superficial vessels and a consequent inflow of blood.

It is also known that certain substances other than heat have analogous characteristics. Various theories have been formulated about the body's mechanism to produce this effect in response to the application of heat and revulsives. According to an early therapeutic scheme, heat and revulsives were used to eliminate the stanching blood and bad humors from the internal organs and to bring them to the surface.

According to the hypothesis of J. Mackenzie, every cutaneous area corresponds to a visceral area which is linked to sympathetic nerve connections. A stimulus, passing to and from a visceral segment by way of the spinal cord, can provoke corresponding vasomotorial reactions of a greater or lesser intensity which can contribute to the cure of a pathological condition.

Other theories attribute the function of these agents to the liberation of histamine to provide the enlargement of the lumen of the vessels. Typical of such prior uses of revulsives are mustard plasters such as those disclosed in U.S. Patent 914,935, issued to Dunn and U.S. Patent 26,719 issued to Titus.

Another prior application of such compounds is disclosed on page 37 of *Merck Index of Chemicals and Drugs*, 7th Edition, by Merck & Co., Rahway, N.J., U.S.A., 1960.

There allyl isothiocyanate, the volatile oil of mustard is described as having a medical use topically in 0.1 to 2% solution in 50% alcohol as a counter-irritant. It indicates a human toxicity in that prolonged contact may cause vesicication and slow-healing ulcers.

Pages 731 and 732 of the Italian text by E. Adami entitled *+ Farmacologia e farmacoterapia-VI Edizione* by Istituto Editoriale Cisalpino-Milano-Varese-1950 indicate that mustard poultices made from mustard flour and warm water work very quickly as a rubefacient causing an acute burning sensation and high hyperaemia of such intensity that they can only be applied to limited areas and for a short time to avoid an intolerable pain and burning sensation. Too long an application would lead to the formation of boils which fester easily and take a long time to heal. This supplements the information presented in the *Merck Index* and indicates that the topical use referred to in the *Merck Index* must be for short periods of time to prevent intolerable pain and burning sensations and to prevent the formation of boils which fester easily and take a long time to heal. This drawback is acknowledged in the *Merck Index* as the noted toxicity.

In practicing my invention, I dissolve oil of horseradish or oil of mustard, as the case may be, in vegetable oil, and I have found that a 2% solution in vegetable oil can be applied for two hours to the body without causing burning or boil formation. These applications can, with care, be repeated twice or thrice daily for several months or once daily for several years.

It is believed that this unexpected result arises from a property of the vegetable oil, which, differently from alcohol, attenuates the revulsive power of oil of mustard or oil of horseradish, by making it tolerable to the surface of the body.

The use of vegetable oil solutions, as claimed, allows the solution to be maintained on the body for a longer period of time, thus allowing the revulsives to enter the dilated pores of the skin and cause reactions in the deep blood vessels of the body underlying the skin to which the solution is applied.

However, apart from these different explanations of the phenomenon, it is clear that while medicine has, until now, been able to provoke these reactions of the superficial vessels, it hasn't been able to produce a similar reaction for the deeper vessels of the human body.

According to the present invention there is provided a new composition and use of oil of mustard or of oil of horseradish (allyl isothiocyanate- C_3H_5NCS), the former one for most patients and the latter for those suffering from nephropathy. Other sources of allyl isothiocyanate, C_3H_5NCS , can also be used, such as cabbage. The composition also contains a

vegetable oil, such as olive oil, peanut oil, corn oil, soya oil or girasol oil.

The drugs are applied by the use of a new technique for obtaining new curative effects.

- 5 The new technique includes the following operations:

impregnate an absorbent dressing with a measured amount of the medicine;

- 10 apply the dressing to a cutaneous surface at the exact point overlying the injured, inflamed, or diathetic organ;

exert pressure on the dressing using the devices described in applicant's U.S. Patent 4,036,229 or U.S. Patent Application Serial No. 885,044 filed March 9, 1978 or U.S. Patent 4,193,401 to Marinello. The disclosure of these patents and applications is incorporated herein by reference. The pressure produced by these devices is applied in such

- 20 a way to get as near as possible to the external cutaneous surface of the body overlying the point of inflammation, or diathesis. This procedure produces the following effects:

the squeezing of the dressing, and releasing

- 25 the solution;

the widening of the pores of the skin subjected to pressure;

the penetration of the solution through the widened pores near the injured, inflamed or diathetic area.

- 30 As a result of the above factors, part of the medicine will reach the blood vessels serving the sick organ, provoking their enlargement, thereby producing an increased flow of blood with curative effects. Such curative effects can be realized when the procedure is followed to cure lower animals as well as humans.

A preferred form of the invention will now be described.

- 40 To increase the blood circulation to an injury, inflammation or diathesis, I propose a remedy utilizing a revulsive with a particular technique. This technique includes the following operations:

- 45 1) Impregnate an absorbent dressing with a measured amount of the revulsive;

2) Apply the dressing to the cutaneous surface at the exact point of the organ which is injured, inflamed, or affected by diathesis;

- 50 3) Exert pressure on the dressing using either the apparatus described in U.S. Patent 4,036,229, dated July 19, 1977 or by using the small inflatable elastic pad described in U.S. Patent Application Serial No. 885,044 filed March 9, 1978. For illnesses regarding the eye socket and the brain one can use the orbital compression chamber, described in U.S. Patent 4,193,401.

- 60 The pressure produced by the above mentioned devices should be applied in such a way as to get as near as possible to the external cutaneous surface of the body at the point of injury, inflammation or diathesis. These operations produce the following ef-

65 fects:

a) the squeezing of the dressing with the resultant expelling of the revulsive medicine;

b) the widening of the pores of the skin subjected to pressure;

- 70 c) the penetration of the medicine through the widened pores near the injured, inflamed, or diathetic area.

As a result of these effects, after entering the pores the medicine will in part disperse into the blood-stream and in part reach the blood vessels serving the injured, inflamed or diathetic organ. This provokes the enlargement of the vessels, thereby producing an increased flow of blood with curative conse-

- 80 quences. One must observe the following precautions regarding the mode of operation:

a') as the medicine is very toxic, it must be diluted and the concentration must be gradually intensified with the progression of the

- 85 cure;

b') during the course of the cure the pressure on the dressing must be increased gradually from an initial minimum, increasing in relation to the improvement of the lesion,

- 90 inflammation or diathesis.

In order most advantageously to effect the enlargement of the blood vessels to aid in the rehabilitation of the affected tissue, a specific revulsive composition has been developed.

- 95 This preferred revulsive uses the oil of mustard (allyl isothiocyanate- C_3H_5CNS) diluted in vegetable oil in a minimum concentration of 1 part of oil of mustard to 1000 parts of vegetable oil up to a maximum concentration of 1 part oil of mustard to 50 parts vegetable oil for the treatment of wounds (including bone wounds), internal inflammation of the human body, and diathesis. The procedure is carried out according to the following directions:

- 105 tions:

a) pour the dilution on an absorbent cotton wool pad dressing;

- 110 b) lay the pad impregnated with the drug on the surface of the skin overlying the internal inflamed, wounded or diathetic part, placing it as near as possible to the injured, inflamed, or diathetic organ;

c) compress the pad against the skin in an affected region of the body.

- 115 The use of the devices described above will press the skin in toward the injured part, dilate the pores of the skin, and release the revulsive from the dressing by squeezing the dressing. The revulsive is forced into the open pores in proximity to the inflamed, wounded, or diathetic organ, to provoke the opening of the blood veins and arteries of the wounded, inflamed, or diathetic organ or tissue and provide a greater blood flow for curative purposes.

- 125 For the treatment of wounds or inflammation of the eye apparatus of the brain, the oil of mustard (allyl isothiocyanate- C_3H_5CNS) should be diluted in vegetable oil in a minimum ratio 1/1000 (1 part oil of mustard and

1000 parts of vegetable oil) up to a maximum ratio 1/80. The procedure is carried out according to the following directions:

- a) Pour the dilution on two absorbent cotton wool dressings;
- b) Mount the two pads on the orbital compression chamber (described in U.S. Patent 4,193,401). Inflate the apparatus as described to expose the external orbital surface to pressure. The squeezing of the two dressings causes them to release the drug through the open pores of the pressurized skin in the proximity of the wounded or inflamed part of the ocular or brain apparatus, thus provoking the opening of the veins and arteries and a greater blood flow to the wounded or inflamed organ for curative purposes.

When used in conjunction with another drug such as an antibiotic, the diluted oil of mustard (allyl isothiocyanate- C_3H_5NCS), when applied as above provides a greater blood flow to the wounded, inflamed, or diathetic part and a greater absorption of the elected drugs.

For patients suffering from nephropathy, a composition containing oil of horseradish, cochlearia armoracia of the family of the Cruciferae, (allyl isothiocyanate- C_3H_5NCS) may be diluted in vegetable oil in the proportions given above for the same purpose and with the same directions for the healing of internal wounds, inflammations and diathesis.

It has also been found that oil of mustard and oil of horseradish may be combined and diluted in vegetable oil for the same purposes and with the same direction as indicated above. It should be remembered that the concentration of the drug should be gradually intensified relative to the improvement of the illness; and the pressure exerted by the above-mentioned apparatus should gradually and progressively increase from an initial minimum, the rate of increase being relative to the rate of healing of the wounds, inflammation or diathesis.

EXAMPLES

The therapeutic results of the composition and the method of applying it can be seen from the following clinical case histories:

Case No. 1 - X-ray Diagnosis

Light, diffuse osteoporosis of the articular cap, wide esophitic apposition of posterior face of the knee-cap.

Treatment

Systematically, for two hours daily and for two months, a compress imbued with mustard oil mixed with vegetable oil (at ratio of 2 gr. of mustard oil and 100 gr. of vegetable oil) was applied to the right knee of the patient and pressed by the elastic inflatable cushion. In the early stages of the treatment, the patient noticed a strong sensation of smarting

in the joint, provoked by the reaction of the blood vessels, caused by the action of the medicine. Gradually this sensation diminished and finally it disappeared. No other therapeutics were practiced.

Results

At the end of the treatment new X-rays disclosed the persistence of arthritis but, at the same time, the total disappearance of the osteoporosis.

Case No. 2

For many years the patient has endured blood pressure problems including at times extremely low blood pressure (highest 90, lowest 50), along with the typical problems attending low blood pressure. A scintillographic examination report stated: "Fairly good view of the suprarenal glands with rhythm of the accumulation sufficiently preserved. The accumulation of the radiomixture was slightly lower on the left. The sudden changes of blood pressure are provoked by irregular emptying of the left suprarenal gland."

After prolonged unfruitful cortisone and cortical hormone therapy, the patient was given the treatment disclosed in this application. The treatment was conducted in the following way: Systematically for two hours on alternative days a compress imbued with oil of horseradish mixed with vegetable oil, at a ratio of 0.4 gr. of the oil of horseradish to 100 gr. of vegetable oil was applied in the loins region and pressed by an elastic inflatable cushion.

After a month of this application the blood pressure was noted as being within normal limits (highest 130, lowest 65) and the patient's problems caused by low blood pressure disappeared. The validity of the treatment was shown both by the disappearance of the symptoms during the treatment and by the reappearance of symptoms (general malaise, deep asthenia, nausea, vertigo) when treatment was suspended for one month. This demonstrated the patient's irreversible hypotrophy of the left suprarenal gland and the impossibility of its complete restoration. The treatment must be continued but makes up for the deficit of the physiological secretion and helps the patient achieve a normal blood pressure and removes the pathological symptoms.

Case No. 3

The patient suffered from prostatic hypertrophy and from chronic cystitis and "pousses" of relapse.

He was treated for three months with the present invention, as follows: A compress imbued with mustard oil mixed with vegetable oil, at a rate of 2 gr. of mustard oil and 100 gr. of vegetable oil, was applied to the perineum and compressed by means of the elastic

inflatable cushion for two hours at a time, three times daily for the first month, twice daily for the second month, and once daily for the third month.

- 5 At the end of this treatment it was possible to notice these advantages: total disappearance of the ischuria and pollakiuria; progressive attenuation of the strangury until it was totally eliminated; total emptying of the vesica
10 and reestablishment of normal urination.

Case No. 4

- X-rays showed a heavy maxillary left sinusitis. A compress imbued with mustard oil and vegetable oil, at a ratio of 1 gr. of mustard oil mixed with 100 gr. of vegetable oil, was applied upon the left cheek and pressed there-
15 against by means of the elastic inflatable cushion, taking care to avoid contact of the compress with the eye. The compress was applied for two hours daily for two months. The advantages of this treatment are: hyperemia and slow general tumefaction of the zone; gradual fluidity of the exudate and reabsorption. The little tumefaction with hyperemia
20 rapidly vanished.

- Thus it can be seen that the composition and method of the present invention achieves therapeutic results in a variety of situations, where increased blood flow to an internal
30 inflammation, injury or diathesis is necessary.

CLAIMS

1. A composition of matter for aiding in the increase of blood flow to an internal injury, inflammation or diathesis comprising allyl isothiocyanate (C_3H_5NCS) and a vegetable
35 oil.

2. A composition as claimed in claim 1 in which the allyl isothiocyanate is present as oil of mustard.
40

3. A composition as claimed in claim 1 in which the allyl isothiocyanate is present as oil of horseradish.
45

4. A composition as claimed in claim 1 and consisting essentially of one part of oil of mustard and from 50 to 1000 parts of vegetable oil.
50

5. A composition as claimed in claim 1 and consisting essentially of one part of oil of mustard and from 80 to 1000 parts of vegetable oil.
55

6. A composition as claimed in claim 1 and consisting essentially of one part of oil of horseradish and from 50 to 1000 parts of vegetable oil.
60

7. A composition as claimed in claim 1 and consisting essentially of one part of oil of horseradish and from 80 to 1000 parts of vegetable oil.
65

8. A composition as claimed in claim 1 and consisting essentially of oil of mustard, oil of horseradish and vegetable oil.

9. A composition as claimed in claim 1 and consisting essentially of mustard, oil of
70

horseradish and 50-1000 parts vegetable oil.

10. A composition as claimed in claim 1 and consisting essentially of one part of allyl isothiocyanate (C_3H_5NCS) and from 50 to 1000 parts of vegetable oil.
70

11. A composition as claimed in claim 1 and consisting essentially of one part of allyl isothiocyanate (C_3H_5NCS) and from 80 to 1000 parts of vegetable oil.
75

12. A composition of matter consisting essentially of the composition of matter claimed in any one of claims 1 to 8 and a therapeutic drug selected for its therapeutic effect on said internal injury, inflammation or
80 diathesis.

13. A composition as claimed in any one of claims 1 to 12 in which the vegetable oil is selected from olive oil, peanut oil, corn oil, soya oil and girasol oil.
85

14. A composition as claimed in claim 1 and substantially as hereinbefore described with reference to any one of the Examples (Cases 1 to 4).
90

15. A method of treating internal injuries, inflammations or diathesis comprising the steps of:-
95

- a) applying a solution containing the composition of any one of claims 1 to 9 to a dressing,
b) positioning said dressing on the cutaneous surface overlying said internal injury, inflammation or diathesis, and
c) exerting sufficient pressure on said dressing to force said cutaneous surface inward
100 towards said injury, inflammation or diathesis, to enlarge the pores of said cutaneous surface and to force said solution into said pores to aid in increasing blood circulation to said internal injury, inflammation or diathesis.

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